Smoking cessation is associated with decreased mortality and improved amputation-free survival among patients with symptomatic peripheral artery disease

Ehrin J. Armstrong, MD, MS,[a] Julie Wu, BS,[b] Gagan D. Singh, MD,[b] David L. Dawson, MD,[c] William C. Pevec, MD,[c] Ezra A. Amsterdam, MD,[b] and John R. Laird, MD,[b] *Aurora, Colo; and Sacramento, Calif*

Objective: **Although smoking cessation is recommended for all patients with peripheral artery disease, there are little data regarding the prevalence of smoking among patients at the time of angiography or the effect of smoking cessation on clinical outcomes.**

Methods: **Consecutive patients with claudication or critical limb ischemia who underwent peripheral angiography from 2006 to 2013 were included in an observational cohort analysis. Smoking status was assessed at the time of angiography and during follow-up clinic visits. Kaplan-Meier analysis was used to assess the relationship between smoking cessation, mortality, and amputation-free survival.**

Results: **Among 739 patients (423 men and 316 women; mean age, 60 ± 12 years), 204 (28%) remained active smokers at the time of lower extremity angiography. At the time of angiography, the mean number of cigarettes smoked per day was 16 ± 10, and the mean pack-years was 40 ± 25. During the course of the subsequent year, 61 patients (30%) successfully quit smoking and maintained continued abstinence. Baseline medication use between groups did not differ significantly. The mean ankle-brachial index was also similar for quitters vs nonquitters (0.53 ± 24 vs 0.49 ± 0.22; $P = .3$). During follow-up to 5 years, patients who quit smoking had significantly lower all-cause mortality (14% vs 31%; hazard ratio, 0.40; 95% confidence interval, 0.18-0.90) and improved amputation-free survival (81% vs 60%; hazard ratio, 0.43, 95% confidence interval, 0.22-0.86) compared with patients who continued smoking, with most of the difference driven by reduced mortality among patients who quit smoking. The findings remained significant on multivariable analysis.**

Conclusions: **Approximately one-third of active smokers with peripheral artery disease successfully quit smoking ≤1 year after lower extremity angiography. Patients who quit smoking have lower mortality and improved amputation-free survival compared with patients who continue smoking. (J Vasc Surg 2014;60:1565-71.)**

Smoking is a major contributor to the development of peripheral artery disease (PAD) and a risk factor for a number of other cardiovascular complications, including coronary artery disease, stroke, and myocardial infarction.[1-4] Among patients with established PAD, continued smoking is also associated with lower rates of lower extremity bypass graft patency and increased risk of amputation.[5,6] Given the established association between smoking and adverse cardiovascular and postsurgical outcomes, immediate smoking cessation is a class I recommendation for all patients with PAD.[7-9]

Despite the known risks of smoking and counseling for smoking cessation, a significant percentage of patients with PAD continue to smoke.[10,11] A number of therapies have been developed to assist with smoking cessation, including nicotine replacement, centrally acting antidepressants (eg, bupropion), and partial agonists of the nicotine receptor (eg, varenicline).[12-14] Even with these medications, most patients with PAD who smoke have low rates of successful cessation during follow-up.

Although smoking cessation is recommended for all patients with PAD, only a few observational studies have examined the relationship between smoking cessation and subsequent cardiovascular and limb-related outcomes.[15-19] These studies suggest that smoking cessation is associated with improved limb-related and cardiovascular outcomes, but the patients studied were from a general population of patients with PAD rather than patients with more advanced lower extremity ischemia. Most of these studies were also conducted before modern smoking cessation therapies were developed. In this study, we assessed the relationship between successful smoking cessation ≤1 year after lower extremity angiography and subsequent cardiovascular and limb-related outcomes.

From the Division of Cardiology, University of Colorado School of Medicine, Aurora[a]; and the Division of Cardiovascular Medicine[b] and Division of Vascular and Endovascular Surgery,[c] and the Vascular Center, University of California, Davis School of Medicine, Sacramento.

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Reprint requests: John R. Laird, MD, UC Davis Vascular Center, 4860 Y St, Ste 3400, Sacramento, CA 95817 (e-mail: john.laird@ucdmc.ucdavis.edu).

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METHODS

The University of California, Davis Medical Center Institutional Review Board approved the protocol for this study, with waiver of informed consent.

Study design and data collection. This was a retrospective study using the PAD-University of California, Davis Registry. This registry includes all patients with PAD and obstructive disease leading to claudication or critical limb ischemia (CLI) who underwent diagnostic lower extremity angiography or endovascular intervention, or both, at the University of California, Davis Medical Center between June 1, 2006, and May 1, 2013.[20] Patients with aneurysmal disease or acute limb ischemia were excluded. All patients in the registry with claudication or CLI were analyzed for this analysis.

Data collection was based on electronic medical record and angiographic review. Demographic, clinical, laboratory, and procedural data were obtained through preprocedure clinical notes, admission history, and in-patient documentation. Also recorded were medical comorbidities, including history of myocardial infarction, stroke, coronary artery disease, and chronic kidney disease. Medications at the time of the procedure were assessed. All records were reviewed by trained chart abstractors and verified by a board-certified cardiologist.

Smoking was assessed by patient self-report in clinic notes. Patients were seen before the procedure in the vascular clinic, where smoking use is routinely quantified. At our institution, any patient seen at the vascular center who is an active smoker is seen by a nurse practitioner dedicated to educating and counseling patients on smoking cessation, with referral to a comprehensive smoking cessation program within our institution. The number of cigarettes smoked per day at the time of angiography was assessed by patient self-report of smoking intensity. Pack-years were derived from patient report of age at which the patient started smoking and the average number of packs smoked per day during that period, which is routinely captured in the electronic medical record.

Abstention from smoking during follow-up was assessed by patient self-report of cessation, which was routinely asked at all follow-up clinic visits. A patient who reported continued abstention from smoking ≤1 year after the lower extremity angiogram was categorized as a successful quitter. Aids to smoking cessation, including use of nicotine replacement and other pharmacologic aids, were assessed by patient report and pharmacy records of drug prescriptions.

The primary study outcome was all-cause mortality. All deaths were confirmed by direct record documentation or the Social Security Death Index.

Myocardial infarction was defined as symptoms of chest pressure and elevation of troponin with evidence of infarct by stress imaging or cardiac catheterization. Stroke was defined as focal neurologic deficit with computed tomography or magnetic resonance imaging evidence of cerebral ischemic or hemorrhagic infarct. Major adverse limb events (MALEs) were defined as major lower extremity limb amputation above the level of the ankle joint, thrombolysis, or surgical bypass.[21] Claudication was classified as Rutherford category 1 to 3 disease (mild, moderate, or severe claudication, respectively), and CLI was classified as Rutherford category 4 to 6 disease (ischemic rest pain, minor tissue loss, or major tissue loss, respectively).[22]

Data analysis. Means with standard deviations are used to describe continuous variables, and frequencies and percentages are used for categoric variables. Continuous variables were compared using the Wilcoxon rank sum test and categoric values using χ^2 or Fisher exact tests. Survival curves for patients who successfully quit smoking vs those who continued smoking were estimated using the Kaplan-Meier method. A Cox proportional hazard model was also developed to assess the relationship between smoking cessation and subsequent outcomes. The final model included adjustment for age, diabetes, coronary artery disease, prior myocardial infarction, glomerular filtration rate, prescription of statin medications, prescription of angiotensin-converting enzyme inhibitors, prescription of β-blocker medications, and baseline ankle-brachial index. All analyses were performed using Stata 13.2 software (Stata Corp LP, College Station, Tex). Hazard ratios (HRs) are provided with 95% confidence intervals (CIs). For all tests, a P value of $<.05$ was considered significant.

RESULTS

Among 739 patients with claudication or CLI referred for lower extremity angiography between 2006 and 2012, 204 (28%) were active smokers. During the course of the subsequent year, 61 patients (30%) successfully quit smoking and maintained continued abstinence (Table I). Compared with nonquitters, quitters were of similar age, sex, and ethnicity, but successful quitters were less likely to have a history of coronary artery disease (26% vs 46%; $P = .007$). Prescription of cardiovascular medications, including aspirin, statin medications, and angiotensin-converting enzyme inhibitors, was similar between groups. The baseline Rutherford classification was not significantly different between groups. The mean ankle-brachial index was also similar for quitters vs nonquitters (0.53 ± 24 vs 0.49 ± 0.22; $P = .3$). Diagnostic lower extremity angiography and subsequent surgical bypass were performed in 23% of patients, and the remainder underwent endovascular intervention. The overall procedural success of patients undergoing endovascular intervention was 93% and did not differ between quitters vs nonquitters (89% vs 95%; $P = .2$). At 30 days after the procedure, the mean improvement in Rutherford classification was similar between quitters vs non-quitters (1.6 vs 1.7; $P = .8$). There were also no differences in quit rates between patients initially presenting with claudication vs CLI (29% vs 30%; $P = .9$).

Among patients who were active smokers at the time of angiography, a mean of 16 ± 10 cigarettes were smoked per day, and the mean pack-years was 40 ± 25. Those who successfully quit smoked a similar number of cigarettes

Table I. Baseline demographics[a]

Variable[b]	*Quit smoking (n = 61)*	*Continued smoking (n = 143)*	P *value*
Age, years	62 ± 10	60 ± 12	.3
Male	32 (52)	86 (60)	.3
Race/ethnicity			.7
Caucasian	54 (89)	129 (90)	
Hispanic	3 (5)	3 (2)	
African American	4 (6)	10 (7)	
Asian	0	1 (1)	
Body mass index, kg/m^2	28 ± 5	27 ± 6	.2
Congestive heart failure	5 (8)	20 (14)	.2
Diabetes mellitus	23 (38)	57 (42)	.6
GFR, mL/min	85 ± 41	88 ± 48	.7
Hypertension	52 (85)	110 (78)	.2
Coronary artery disease	16 (26)	66 (46)	.007
COPD	13 (21)	40 (29)	.3
History of			
Myocardial infarction	11 (18)	25 (17)	.9
Stroke/TIA	6 (10)	25 (17)	.2
Malignancy	5 (8)	14 (10)	.7
AAA	4 (7)	4 (3)	.2
Carotid stenosis	5 (9)	21 (16)	.1
Contralateral amputation	2 (3)	16 (11)	.2
Medication use			
Statin	33 (54)	83 (58)	.6
Aspirin	54 (88)	123 (86)	.7
β-blocker	24 (39)	71 (50)	.2
ACE inhibitor	34 (55)	72 (50)	.5
Rutherford score			.8
1	3 (5)	6 (4)	
2	10 (16)	31 (22)	
3	13 (21)	26 (18)	
4	5 (8)	19 (13)	
5	25 (41)	47 (33)	
6	5 (8)	12 (8)	
Ankle-brachial index[c]	0.49 ± 0.22	0.54 ± 0.23	.3
Type of procedure performed			.1
Diagnostic only	18 (30)	29 (20)	
Femoropopliteal	20 (33)	37 (26)	
Infrapopliteal	23 (38)	76 (53)	
Procedural success	42 (89)	110 (95)	.2

AAA, Abdominal aortic aneurysm; *ACE*, angiotensin-converting enzyme; *COPD*, chronic obstructive pulmonary disease; *GFR*, glomerular filtration rate; *TIA*, transient ischemic attack.

[a]Procedural success is reported among the subgroup of patients who underwent endovascular intervention.

[b]Continuous data are reported as mean ± standard deviation and categoric data as number (%).

[c]Noncompressible values were excluded.

Table II. Smoking habits among quitters vs nonquitters

Variable[a]	*Quit smoking (n = 61)*	*Continued smoking (n = 143)*	P *value*
Cigarettes smoked per day	15 ± 12	16 ± 10	.7
Pack-years	44 ± 37	36 ± 22	.04
Attempted quitting	61 (100)	34 (25)	<.001
Type of cessation aid			.8
Nicotine replacement	4 (7)	15 (10)	
Varenicline	3 (5)	10 (7)	
Bupropion	1 (2)	4 (3)	
None	53 (87)	114 (80)	

[a]Continuous data are reported as mean ± standard deviation and categoric data as number (%).

per day at the time of angiography (15 ± 12 vs 16 ± 10 daily; $P = .7$), but had significantly greater average pack-year smoking history (44 ± 37 vs 36 ± 22 pack years; $P = .04$) than nonquitters. Only a minority of patients used smoking cessation aids such as nicotine replacement or other pharmacologic agents (Table II). Among patients who failed to quit smoking, 25% attempted to quit in the subsequent year but ultimately resumed smoking.

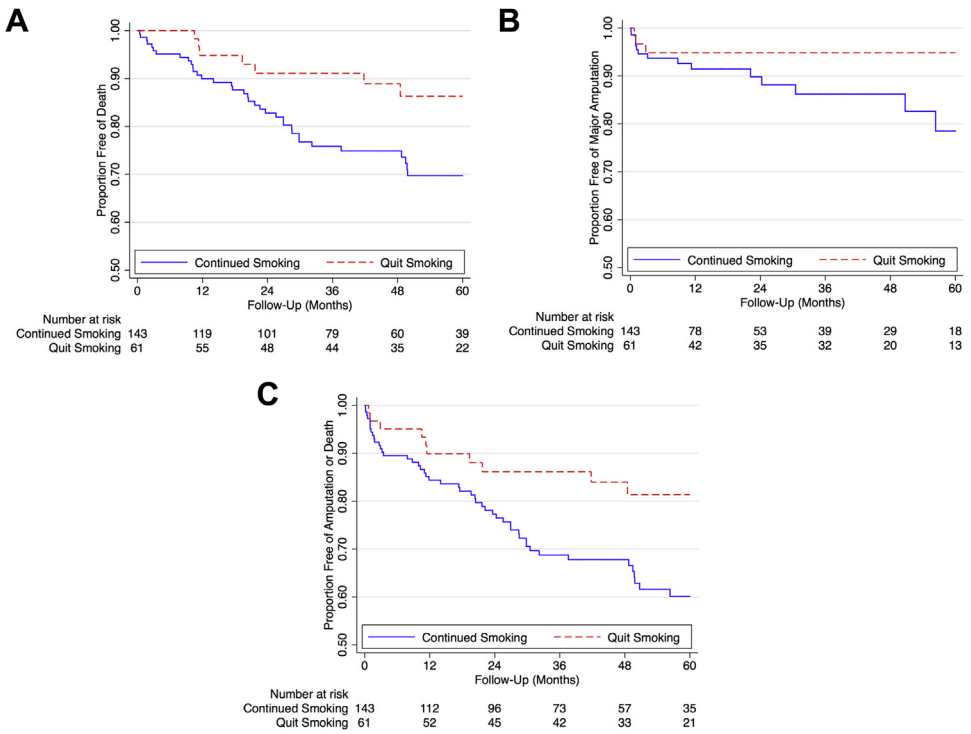

Fig 1. Kaplan-Meier curves show **(A)** mortality, **(B)** rates of major amputation, and **(C)** amputation-free survival among patients who continued (*solid line*) vs quit (*dashed line*) smoking.

In unadjusted analyses, patients who were nonsmokers at the time of lower extremity angiography had lower rates of 5-year mortality (HR, 0.66; 95% CI, 0.47-0.93) but similar rates of major amputation (HR, 0.85; 95% CI, 0.50-1.45) and amputation-free survival (HR, 0.76; 95% CI, 0.57-1.03) compared with patients who were active smokers at the time of angiography. This difference in outcomes based on initial smoking status was explained by improved outcomes among patients who subsequently quit smoking vs continued poor outcomes among patients who continued smoking.

During follow-up to 5 years after the procedure, patients who quit smoking ≤1 year after lower extremity angiography had significantly lower unadjusted rates of all-cause mortality (absolute event rate of 14% vs 31%; HR, 0.40; 95% CI, 0.18-0.90) and improved amputation-free survival (absolute event-free rate of 81% vs 60%; HR, 0.43; 95% CI, 0.22-0.86) compared with patients who continued smoking (Fig 1). Event rates of myocardial infarction, stroke, major amputation, and MALEs also all favored smoking cessation, although these individual end points were not statistically significant. Similar results were observed when the analysis was limited to the 414 patients who initially presented with CLI, of whom 107 were active smokers at the time of angiography. A significantly reduced risk of mortality and improved amputation-free survival was noted among patients with CLI who quit smoking (Fig 2), although most of the difference in amputation-free survival was driven by lower mortality among the patients who successfully quit smoking.

Univariate analysis revealed several other predictors of mortality and major amputation among active smokers at the time of lower extremity angiography, including age, diabetes, coronary artery disease, prior myocardial infarction, and ankle-brachial index (Table III). On multivariable analysis after adjusting for age, medical comorbidities, and other medical treatment, smoking cessation remained associated with a significantly reduced mortality (adjusted HR, 0.33; 95% CI, 0.13-0.80), improved amputation-free survival (adjusted HR, 0.40; 95% CI, 0.19-0.83), and a nonsignificant trend toward benefit for other secondary outcomes (Table IV). Similar point estimates were obtained on multivariable analysis among patients with CLI.

DISCUSSION

In this study, we assessed the relationship between successful smoking cessation during the year after lower extremity angiography among patients with lifestyle-limiting claudication or CLI. Our major findings were that one-third of long-term smokers successfully quit in the year after angiography and that successful smoking cessation was associated with significantly decreased mortality and improved amputation-free survival during 5 years of follow-up. These findings remained significant after multivariable adjustment, suggesting that successful smoking

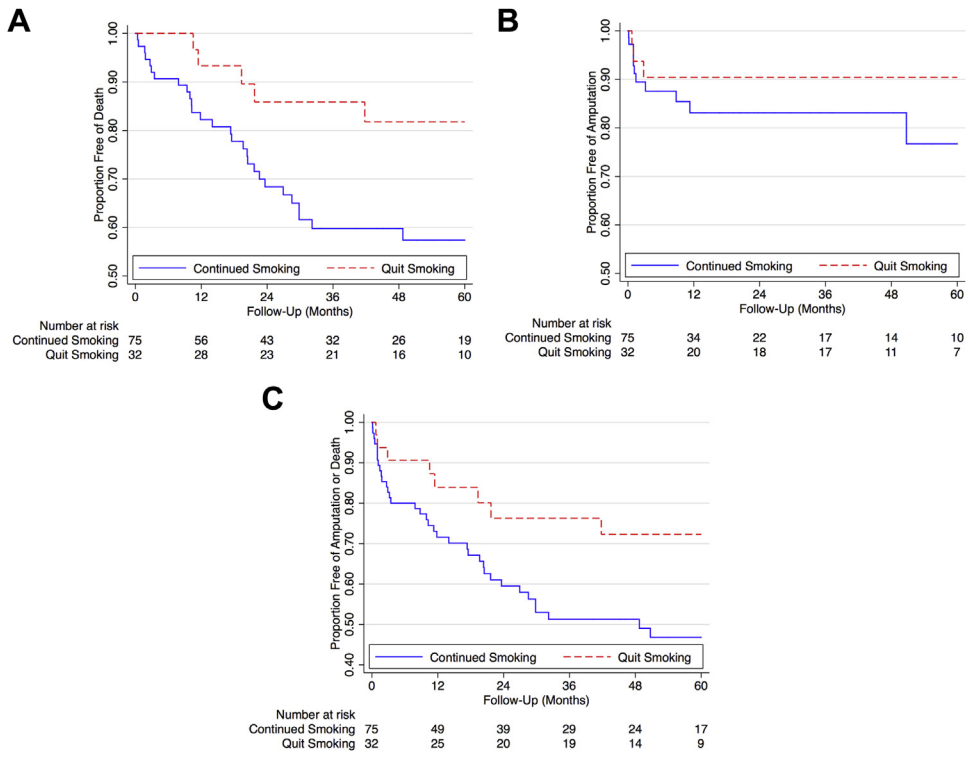

Fig 2. Kaplan-Meier curves show **(A)** mortality, **(B)** rates of major amputation, and **(C)** amputation-free survival among patients with critical limb ischemia (CLI) who continued (*solid line*) vs quit (*dashed line*) smoking.

Table III. Univariate associations for mortality and major amputation among active smokers at the time of lower extremity angiography

	Mortality		*Major amputation*	
Variable	*HR (95% CI)*	P *value*	*HR (95% CI)*	P *value*
Smoking cessation	0.40 (0.18-0.90)	.03	0.38 (0.11-1.31)	.1
Age	1.04 (1.03-1.05)	.001	0.99 (0.97-1.01)	.3
Male gender	1.16 (0.88-1.53)	.3	0.73 (0.45-1.18)	.2
Diabetes	1.38 (1.04-1.83)	.03	2.64 (1.57-4.44)	.001
Coronary artery disease	1.54 (1.16-2.04)	.003	1.06 (0.66-1.69)	.8
Myocardial infarction	1.70 (1.23-2.34)	.001	1.71 (1.02-2.87)	.04
Statin medications	0.77 (0.57-1.02)	.07	0.54 (0.34-0.85)	.009
ACE inhibitors	0.80 (0.60-1.06)	.1	0.64 (0.40-1.02)	.06
β-blocker medications	1.71 (1.30-2.32)	.001	1.56 (0.97-2.52)	.07
GFR	0.98 (0.97-0.98)	.001	0.99 (0.98-0.99)	.02
Ankle-brachial index	0.11 (0.04-0.31)	.001	0.10 (0.02-0.51)	.006

ACE, Angiotensin-converting enzyme; *CI*, confidence interval; *GFR*, glomerular filtration rate; *HR*, hazard ratio.

cessation is independently associated with decreased mortality among patients with claudication or CLI.

At the time of the initial lower extremity angiography, 28% of patients in the overall cohort were active smokers. All of the patients in this study were followed up in a multidisciplinary vascular clinic where smoking cessation counseling is routinely provided. The decision to pursue lower extremity angiography and possible endovascular intervention among active smokers with claudication is controversial, because continued smoking is associated with progression of PAD and decreased graft patency. Among patients with CLI, the presence of a threatened limb may necessitate angiography and intervention, regardless of smoking status.

We found no difference in the baseline presentation or severity of disease among patients who quit vs continued smoking, suggesting that successful quitting was not driven by patient symptoms of continued lower extremity ischemia. In fact, the only significant demographic difference between quitters vs nonquitters was a lower prevalence of coronary artery disease among patients who successfully quit. These findings and prior studies suggest

Table IV. Unadjusted and adjusted 5-year outcomes among patients who quit smoking

	Event rate, % (95% CI)			
Outcome	*Quitters*	*Nonquitters*	*Unadjusted HR (95% CI)*	*Adjusted HR (95% CI)*[a]
Mortality	14 (7-27)	31 (23-40)	0.40 (0.18-0.90)	0.33 (0.13-0.80)
Amputation-free survival	81 (10-32)	60 (31-50)	0.43 (0.22-0.86)	0.40 (0.19-0.83)
Myocardial infarction	8 (3-20)	16 (8-31)	0.72 (0.22-2.31)	0.68 (0.20-2.30)
Stroke	2 (1-14)	5 (2-15)	0.44 (0.10-3.98)	0.58 (0.10-5.60)
Major amputation	7 (2-15)	22 (12-37)	0.38 (0.11-1.31)	0.43 (0.12-1.57)
MALE	33 (21-49)	31 (19-45)	1.40 (0.80-2.70)	1.40 (0.69-2.82)

CI, Confidence interval; *HR,* hazard ratio; *MALE,* major adverse limb event.
[a]Includes adjustment for age, diabetes, coronary artery disease, prior myocardial infarction, glomerular filtration rate, prescription of statin medications, prescription of angiotensin-converting enzyme inhibitors, and prescription of β-blocker medications.

that psychologic factors and patient readiness to quit, rather than overall health status, may play a larger role in successful smoking cessation.[23]

During the course of 1 year after lower extremity angiography, approximately one-third of active smokers successfully quit smoking and maintained abstinence from smoking. Prior studies of smoking cessation in the general population have reported low overall rates of successful abstinence, ranging from 5% with counseling to 30% with more recent pharmacologic approaches.[13,14] Most of these studies have reported 6-month rates of abstention, which may be higher than 1-year rates of smoking abstinence. In the only randomized trial of intensive smoking cessation counseling among patients with PAD, intensive counseling resulted in a successful abstinence rate of 21% vs 6.8% in the control group.[11] Only a minority of patients in our cohort used counseling or adjunctive pharmacologic aids. The reasons for this are uncertain, but prior studies have suggested that many patients are hesitant to use pharmacologic therapies to assist with smoking cessation.[24] These findings suggest that the time of first angiography among patients with PAD is an opportunity to further reinforce the benefits of smoking cessation. It is possible that a more structured intervention at the time of lower extremity angiography and the months afterward could possibly successfully increase rates of quitting to a higher level than we observed in this observational study.

Most of the benefit from smoking cessation was reflected by reduced overall mortality, with an absolute mortality of 14% at 5 years among successful quitters vs 31% among patients who continued smoking. This mortality benefit was even more apparent among the subgroup of patients with CLI, where the absolute 5-year mortality rates were 18% vs 43% ($P = .03$). To our knowledge, this study is the first systematic investigation of the benefits of smoking cessation among patients with CLI. Given the high mortality of patients with CLI, smoking cessation may have particular benefit in these patients, especially because the benefits of smoking cessation extended to amputation-free survival. Although there was no difference in MALEs among patients who quit vs continued smoking, this was likely due to the higher rates of lower extremity bypass performed among patients who successfully quit smoking. Given the known association between smoking and early graft failure, the differential rates of surgical bypass are likely related to physician decision making.[25] A larger study would likely be necessary to detect significant differences in rates of major amputation among patients who quit vs continued smoking.

This study has several limitations: First, this was an observational cohort study. Other unmeasured confounders might possibly account for the apparent differences in outcomes among patients who quit smoking vs those who continued smoking.

Second, we relied on patient self-report of smoking cessation. It is possible that patients under-reported their cigarette intake or did not actually quit smoking. However, the presence of continued smokers in the cohort of patients considered to have quit would bias the results towards the null, thereby suggesting that our findings remain valid.

Third, the small size of the overall cohort likely resulted in nonsignificant findings regarding the effects of smoking cessation on myocardial infarction, stroke, and other secondary outcomes. Smoking cessation would likely be associated with a benefit for each of these end points if studied in a larger cohort.

CONCLUSIONS

One-third of active smokers with claudication or CLI successfully quit smoking in the year after lower extremity angiography. Successful smoking cessation was associated with decreased mortality and improved amputation-free survival during follow-up to 5 years. These findings should provide additional impetus to encourage smoking cessation among all patients with PAD.

AUTHOR CONTRIBUTIONS

Conception and design: EJA, JW, GS, DD, WP, EAA, JL
Analysis and interpretation: EJA, JW, GS, DD, WP, EAA, JL
Data collection: EJA, JW, GS
Writing the article: EJA, JW, JL
Critical revision of the article: EJA, JW, GS, DD, WP, EAA, JL

Final approval of the article: EJA, JW, GS, DD, WP, EAA, JL
Statistical analysis: EJA, JW
Obtained funding: JL
Overall responsibility: JL

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